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**PALLADIUM-CATALYZED SELECTIVE AND SEQUENTIAL
FUNCTIONALIZATION OF 2,4,6-TRIHALOPYRIDINE RINGS:
SYNTHESIS OF ETHYNYLPYRIDINE POLYMERS DIRECTLY JOINED
WITH AZA-CROWN ETHERS**

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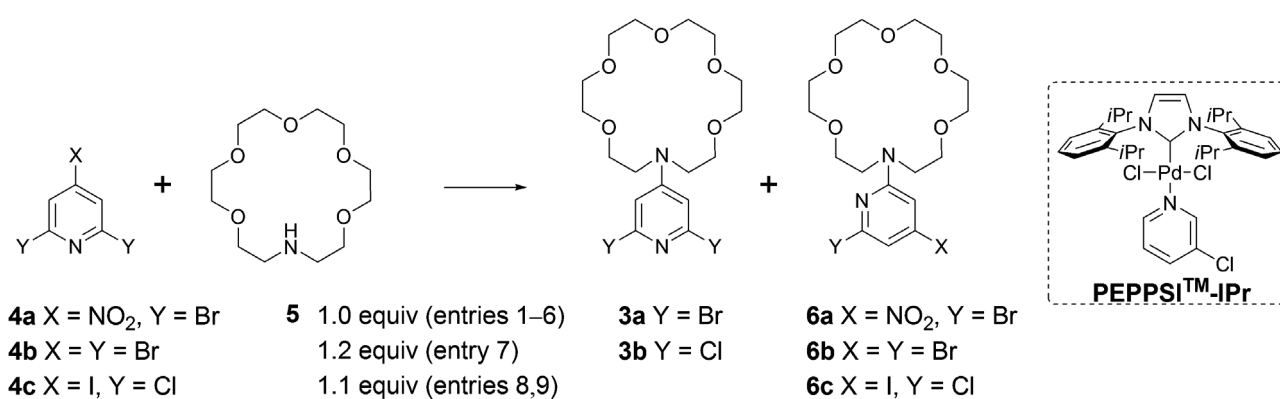
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Abstract – *meta*-Ethylnylpyridine polymer *directly* joined with 1-aza-18-crown-6 ether was synthesized by applying 2,4,6-trihalopyridines as a starting material. By using a Pd(OAc)₂-BINAP combination with an excess of Cs₂CO₃, 2,6-dichloro-4-iodopyridine could be condensed with 1-aza-18-crown-6 ether to afford 4-azacrown-substituted 2,6-dichloropyridine selectively. The two chlorine atoms of this product were replaced with ethynyl groups by copper-free Sonogashira reaction with *tert*-butyldimethylsilylacetylene followed by protidesilylation. Subsequent steps involving Sonogashira reactions gave diiodo- and diethynyl- substituted tripyridine units, and their co-polymerization yielded the targeted polymer.

Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

Crown ethers represent a class of the most commonly used host molecules, which can associate with a variety of cationic species through electrostatic interactions.¹ This characteristic has attracted chemists to the development of molecular devices possessing crown ethers as a functional moiety.^{2,3} For example, Yashima *et al.* and Kakuchi *et al.* reported the helicity induction on polymers regulated by host-guest interaction between crown ethers and amino acids.³ Thus, an efficient synthetic strategy for introducing crown rings on organic frameworks is valuable in the progress of supramolecular chemistry.

presence of a strong base (Table 1, entries 1–4). The secondary amino group in **5** has only weak nucleophilicity because of the transannular steric hindrance and the coordination with the metal cations of the bases. Next, we attempted palladium-catalyzed amination methodologies. When non-nucleophilic strong base (LiHMDS) and highly active Pd complex PEPPSITM-IPr were applied,⁵ the azacrown moiety could be introduced on the pyridine ring of **4b** (Table 1, entry 5). Unfortunately, not only the desired 4-substituted product but also undesired 2-substituted one was obtained as a difficultly separable mixture. Changing the reactivity of each halogen atom, we subjected 2,6-dichloro-4-iodopyridine (**4c**)⁶ to a similar amination. Although the combination of LiHMDS and PEPPSITM-IPr could not improve the selectivity

Table 1. Optimization of the amination reaction of **4**

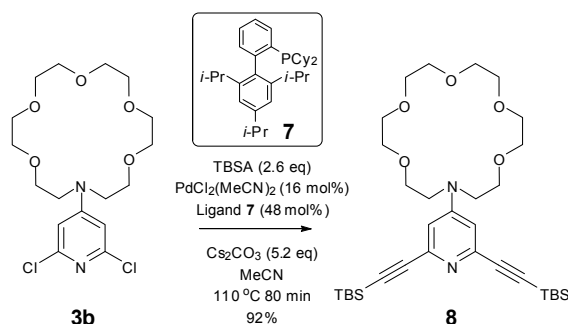
entry	substrate	conditions		solvent	product [%]	
		reagents			3a	6a
1	4a	NaH (1.1 eq)		DMF	3a n.d. ^a	6a n.d. ^a
2	4a	<i>t</i> -BuOK (1.1 eq)		THF	3a n.d. ^a	6a n.d. ^a
3	4b	NaH (1.1 eq)		DMF	3a n.d. ^a	6b n.d. ^a
4	4b	<i>t</i> -BuOK (1.1 eq)		THF	3a n.d. ^a	6b n.d. ^a
5	4b	LiHMDS (2.0 eq)/PEPPSI TM -IPr (2 mol%)		toluene	3a 29 ^b	6b 13 ^b
6	4c	LiHMDS (2.0 eq)/PEPPSI TM -IPr (2 mol%)		toluene	3b 28 ^b	6c 20 ^b
7	4c	Cs ₂ CO ₃ (5.0 eq)/Pd(OAc) ₂ (4 mol%)/(±)-BINAP (4 mol%)		toluene	3b 49 ^c	6c n.d. ^a
8	4c	<i>t</i> -BuOK (1.2 eq)/PEPPSI TM -IPr (2 mol%)		DME	3b n.d. ^a	6c n.d. ^a
9	4c	<i>t</i> -BuOLi (1.2 eq)/PEPPSI TM -IPr (2 mol%)		DME	3b n.d. ^a	6c n.d. ^a

^a Not detected. ^b Determined by ¹H NMR. ^c Isolated yields.

LiHMDS = lithium bis(trimethylsilyl)amide, BINAP = bis(diphenylphosphino)-1,1'-binaphthyl, DME = 1,2-dimethoxyethane.

(Table 1, entry 6), the use of a Pd(OAc)₂-BINAP combination with a large excess of Cs₂CO₃⁷ did work, yielding 4-substituted product **3b** as a sole product (entry 7).⁸ The use of alkali butoxides gave no coupling product (entries 8,9).

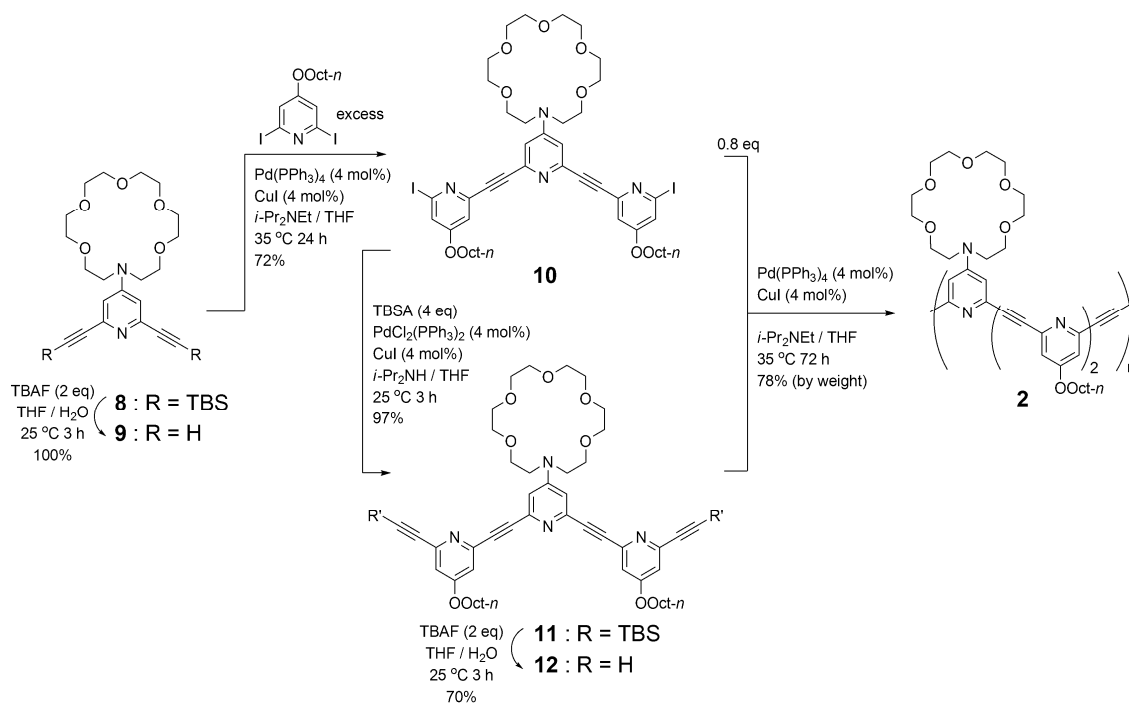
Subsequently, the remained two chlorine atoms were subjected to Sonogashira reaction. When Buchwald's copper-free procedure⁹ was applied to **3b**, bis(*tert*-butyldimethylsilylethynyl) product **8** could be obtained in 92% yield without disturbance by the bulky azacrown rings (Scheme 1).¹⁰ The co-polymer **2** was prepared as shown in Scheme 2. After protodesilylation of **8**, the obtained **9** was extended to co-trimeric diiodide **10** with the treatment of an excess of 2,6-diiodo-4-octyloxy pyridine.¹¹ Further diethynylation of **10** gave **12**, which was used as the counterpart of **10** at the final step. The co-polymerization between the diiodide **10** and the diacetylene **12** was carried out by Sonogashira reaction as shown in Scheme 2 to give the co-polymer **2** (*M_n* = 120,000 g/mol vs polystyrene standards), which was identified on the basis of ¹H NMR.¹²



Scheme 1. Sonogashira reaction of **3b** to **8** by Buchwald's copper-free procedure

TBSA = (*tert*-butyldimethylsilyl)acetylene

In summary, we succeeded in preparing a new type of ethynylpyridine polymer that has 1-aza-18-crown-6 rings directly attached to the pyridine rings at the 4-positions. In that connection, we developed a selective and sequential functionalization of 2,4,6-trihalopyridine. The use of Pd(OAc)₂ with BINAP and Cs₂CO₃ proved to selectively afford 4-azacrown-substituted 2,6-dichloropyridine in moderate yield. The remained two chlorine atoms could successively be alkynylated by Sonogashira reaction according to Buchwald's copper-free procedure. The targeted polymer was obtained by the stepwise co-polymerization of the azacrown-attached pyridine units and the octyloxy-attached pyridine units by usual Sonogashira reactions. The co-polymer has potential as a host molecule, the higher-order structures of which could more effectively be regulated by the addition of guest cationic species. Such study about the saccharide recognition ability and heteroallosterism caused by the guest is underway.

Scheme 2. Preparation of co-polymer **2**

TBAF = tetrabutylammonium fluoride, TBSA = (*tert*-butyldimethylsilyl)acetylene

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 - Preparation of **3b**. To a toluene (15 mL) solution of Pd(OAc)₂ (14 mg, 60 μmol) and (±)-BINAP (37 mg, 60 μmol) were added 2,6-dichloro-4-iodopyridine (**4c**) (0.42 g, 1.6 mmol), 1-aza-18-crown-6 (0.48 g, 1.8 mmol), and Cs₂CO₃ (2.4 g, 7.5 mmol). The reaction mixture was stirred for 5 min at room temperature and 12 h under reflux. After cooling to room temperature, the resulting mixture was filtered. The filtrate was concentrated by a rotary evaporator and purified by silica gel column chromatography (eluent: CH₂Cl₂/MeOH = 97:3) to yield **3b** (0.31 g, 49%) as a yellowish brown oil. IR (neat) ν_{\max} 2869, 1584, 1517 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.52 (s, 2 H), 3.74–3.60 (m, 24 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.0, 150.5, 104.9, 70.9, 70.7, 70.6, 68.1, 51.1, 27.5; HRMS (ESI) Calcd for C₁₇H₂₇Cl₂N₂O₅ (M + H⁺): 409.1297; Found: 409.1301.
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 - Preparation of **8**. A mixture of **3b** (3.0 g, 7.3 mmol), PdCl₂(MeCN)₂ (0.3 g, 1.2 mmol), ligand **7** (1.7 g, 3.5 mmol), and Cs₂CO₃ (12 g, 38 mmol) in MeCN (120 mL) was stirred for 30 min at room temperature, then *tert*-butyldimethylsilylacetylene (2.7 g, 19 mmol) was added to the mixture dropwise. The reaction mixture was stirred for 80 min under reflux. After cooling to room temperature, the resulting mixture was diluted with ether (200 mL) and filtered through a pad of Florisil. The filtrate was evaporated by a rotary evaporator and purified by silica gel column chromatography (eluent: CH₂Cl₂/MeOH = 97:3) to yield **8** (4.1 g, 92%) as a brown oil. IR (neat) ν_{\max} 2951, 2927, 2856, 2155, 1581, 1523 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.68 (s, 2 H), 3.78–3.58 (m, 24 H), 0.98 (s, 18 H), 0.18 (s, 12 H); ¹³C NMR (75 MHz, CDCl₃) δ 152.6, 143.0, 110.0, 105.1, 91.0, 70.8, 70.63, 70.58, 68.2, 50.4, 26.2, 16.7, -4.6; HRMS (ESI) Calcd for C₃₃H₅₇N₂O₅Si₂ (M + H⁺): 617.3806; Found: 617.3834.
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 - ¹H NMR (300 MHz, CDCl₃) δ 7.13 (br s, 4n H), 6.90 (br s, 2n H), 4.02 (br s, 4n H), 3.67 (br s, 24n H), 1.78 (br s, 4n H), 1.52–1.18 (m, 20n H), 0.90 (br s, 6n H).